ORIGINAL RESEARCH PAPER

Anaesthesiology

COMPARISON OF TWO DIFFERENT DOSES OF INTRATHECAL CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE FOR LOWER LIMB ORTHOPAEDIC SURGERIES: A PROSPECTIVE RANDOMIZED DOUBLE BLINDED STUDY

KEY WORDS: Intrathecal Clonidine, Hyperbaric Bupivacaine, Lower Limb, Orthopaedic

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ABSTRACT

Background - Intra thecal clonidine is used as an adjuvant to local anesthetic for prolonging the duration of analgesia . The aim of the study was to evaluate and compare the efficacy of intrathecal clonidine in doses of 15 mcg and 30 mcg added to 0.5% hyperbaric bupivacaine (15mg) in spinal anaesthesia for lower limb orthopaedic surgeries . **Methodology –** A total of 120 patient were randomly divided into two groups . Group I received 3ml (15mg) of 0.5% hyperbaric bupivacaine with 0.1 ml clonidine (15mcg) and 0.1 ml normal saline. And Group II received 3ml (15mg) of 0.5% hyperbaric bupivacaine with 0.2 ml clonidine (30 mcg) .We compared the groups in terms of onset and duration of sensory and motor block , duration of analgesia , hemodynamics and side effects . **Result –** The difference in group I and II with regard to onset of sensory block was statistically significant (p=0.002) .The average onset of motor block , total duration of sensory and motor block showed statistically significant value (p=0.000) . The time of first rescue analgesia was prolonged in group II (298.67+14.75 min) as compared to group I (272.08+16.37 min). The difference in fall in mean arterial pressure (MAP) was statistically significant after 20 minutes of induction. Hypotension was observed in 5 patients in group I and 7 patients group II , but it was not statistically significant . Bradycardia and sedation in both the groups was not statistically significant . **Conclusion -** 30 mcg was better than 15 mcg in prolonging the sensory block, motor block and duration of analgesia, with no significant adverse effect .

Introduction –

Spinal anaesthesia was first performed by August Bier on 16th august 1898 when he injected 3 ml of 0.5 % cocaine intrathecally into a 34-year-old laborer.[1] Since then it has been extensively used as it is safe and reliable technique. It provides effective sensory and motor blockade as well as post-operative pain relief. The extent of neural blockade produced by spinal anaesthesia depends on local anesthetics and adjuvant used. Hyperbaric bupivacaine (0.5 %) which is an amide local anesthetic is commonly used intrathecally in lower limb orthopedic surgeries. However, the duration of spinal anaesthesia with bupivacaine does not last beyond 2.5 to 3.0 hours with local anesthetic alone.[2] Adding adjuvant drugs to intrathecal bupivacaine improves the quality and duration of spinal anaesthesia and prolongs post-operative analgesia. Different opioids and non-opioids have been tried as an additive with variable results.[3] It has been reported that hyperbaric bupivacaine combined with opioids like fentanyl produces reliable spinal anaesthesia. Unfortunately, this combination resulted in incidence of respiratory depression and pruritus.[4,5] Therefore, different non opioids like 2 adrenergic agonists have been evaluated because of their sedative, analgesic and hemodynamic stabilizing effect in neuroaxial anaesthesia. Clonidine being an alpha 2 adrenergic agonist is known to have potent antinociceptive properties by various mechanism at spinal and supra spinal level including the ability to potentiate the effects of local anesthetics.[6][7] The mechanism behind the prolongation of motor and sensory block by clonidine is not very well known. It attenuates analgesia by depressing the release of C-fiber transmitters and by hyper polarization of postsynaptic dorsal horn neurons. Binding of clonidine to motor neurons in the dorsal horn prolong motor block.[8] Clonidine is a sedative, anti-emetic, anxiolytic and reduces post-operative shivering.[9] Uncontrolled post-operative pain may produce a range of detrimental acute and chronic effects. Intrathecal clonidine prolongs the sensory blockade and also produces post-operative analgesia. There are different studies comparing various doses of clonidine ranging from 15 mcg to 150 mcg as an adjuvant to local anesthetic for spinal anaesthesia. At higher doses, it increases the duration of anaesthesia but may have hemodynamic side effects.We therefore compared two low doses of clonidine.

Methodology –

This was a hospital based prospective randomized double blinded study conducted among 120 patients who underwent lower limb orthopedic surgeries under spinal anaesthesia in a Tertiary Heath Care Centre, after obtaining clearance from Institutional Ethics Committee. We included normotensive patients of ASA grade I and II of either sex, 18 to 55 year age group posted for lower limb orthopedic surgeries under spinal anesthesia .We excluded the patients of ASA grade III and IV , patients with any allergy to drug , pregnant patients , patients with cardiovascular, renal or hepatic diseases, and patients with any contraindication to spinal anaesthesia . Patients requiring supplementation with general anaesthesia were excluded from study . According to data reported in Arora R et al [10] sample size of 98 was calculated. But accounting for 20% dropout, a final sample size was 120. Patients were randomly divided into two group (n =60) using computer generated randomization table . The assigned group was enclosed in a sealed envelop to ensure concealment of allocation group . All the patients which needed lower limb orthopedic surgeries went through detailed pre anesthetic evaluation which include history, general examination , systemic examination . Spine was examined for deformity or infection . All routine investigations were done. The patients who met the inclusion criteria were considered for the study . The anesthetic procedure was briefly explained to the patient and informed written consent was obtained . The patient was explained Visual Analogue Scale system pre operatively . Patient were kept nil by mouth for 8 hrs before surgery .

On the day of surgery after shifting the patient to the operating room, intra venous line was secured and I.V preloading with Ringer lactate (10ml/kg) was started . The patient were connected to a monitor (Phillips Intellivue MP50) which included non invasive blood pressure monitor , pulse

oximeter and electrocardiogram. Baseline parameters like heart rate (HR) , MAP were recorded. The anesthesiologist not involved in the study opened the sealed envelop in the operation theatre, allocated the patient to the respective group and prepared the study drug accordingly . The procedure and observation was done by the anesthesiologist who was blinded to the study drug . The patients were also blinded to the study group . Patients were allocated into two groups . Group I (n=60) received 3ml (15mg) of 0.5% hyperbaric bupivacaine with 0.1 ml clonidine (15mcg) and 0.1 ml normal saline. Group II (n=60) received 3ml (15mg) of 0.5% hyperbaric bupivacaine with 0.2 ml clonidine (30 mcg) .Each group received 3.2 ml of intrathecal injection.

Under all aseptic precaution subarachnoid block was performed in sitting position in midline approach at L3-L4 level using a 25G Quincke spinal needle. After confirming the free flow of csf , the drug was injected at a rate of 0.2 ml/sec ,the spinal needle was taken out . Thereafter patients were kept in supine position and operating table was kept horizontal .

The Study parameters observed are -
1.Onset of sensory block -The time between injection of intrathecal anesthetic and the absence of pain at the T10 dermatomes, assessed by pinprick.

2.Maximum level of sensory block - Sensory block was recorded every 5 min after intrathecal injection till 20 min and highest level was observed.

3.Duration of sensory block- Time of regression of two segments in the maximum block height.

4.Motor block – the motor blockage was assessed using modified Bromage scale.

Modified Bromage scale is followed accordingly: 0– patient able to raise the whole lower limb at the hip, 1– patient able to flex the knee but unable to raise the leg at hip ; 2– patient able to plantar flex ankle but unable to flex the knee ; 3– no movement of lower limb by patient .

The complete motor block was considered when Bromage score became three.

5.Complete motor block recovery was considered when Bromage score became zero.

6.Duration of analgesia (Time to analgesic request) - from spinal injection to the first occasion when the patient complaints of pain. (VAS score > 4) .

7.Haemodynamics- MAP, HR and SpO2 were recorded 5 min before intrathecal injection and then every 5 minutes for first 30 minutes and then every 15 minutes till the end of the surgery. Hypotension (fall in mean arterial pressure > 20 % of the baseline) was treated with intravenous fluids and i.v. ephedrine 6 mg in incremental doses .Bradycardia (HR < 50 beats/min), was treated with 0.6 mg of i.v. atropine sulphate.

8.Post operatively – HR, MAP and SpO2 were monitored in the post-operative care unit. Pain scores using VAS was noted, and intravenous paracetamol 15 mg/kg was given when VAS score was > 4 .Time to first rescue analgesic was noted (TFRA).

9.The side effects of intrathecal clonidine like bradycardia, hypotension, sedation, and others if any were noted.

10.Sedation was assessed using Ramsay Sedation Scale .

Statistical analysis was performed using SPCC version 20 (USA). Descriptive statistic was done for all data. Categorical variable were expressed as actual numbers and percentages. Continuous variables were expressed as mean and standard deviations . Parametric variables were analyzed with student's t-test .While for non parametric data chi-square test was used. P < 0.005 was considered statistically significant and p < 0.001 as highly significant .

Results –

Table 1

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
OSB	I	60	4.42	.696	.090	0.002
	II	60	4.02	.701	.090	
ONSET OF SENSORY BLOCK (IN MINUTE)						
	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
OMB	I	60	7.48	.748	.097	0.000
	II	60	6.72	.904	.117	
ONSET OF MOTOR BLOCK (IN MINUTE)						

Table 2

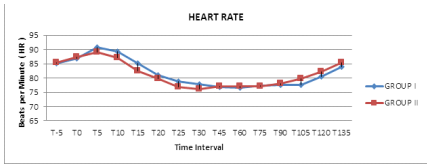
	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
DSB	I	60	122.00	9.966	1.287	0.000
	II	60	130.08	7.277	.939	
DURATION OF SENSORY BLOCK (IN MINUTES)						
	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
	I	60	184.08	16.887	2.180	0.000
	II	60	200.67	11.330	1.463	
DURATION OF MOTOR BLOCK (IN MINUTES)						

The average onset of sensory block in Group I was 4.42 minute and for group II was 4.02 minutes. (p = 0.002). Average onset of motor block in Group I was 7.48 minutes and for Group II it was 6.42 minutes. The total duration of sensory block in Group I was 122 minutes and for group II it was 130.08 minutes. Duration of motor block in Group I was 184.08 minutes and for group II it was 200.67 minutes .On comparing the both groups, p value was 0.000. This denotes that difference was highly significant.

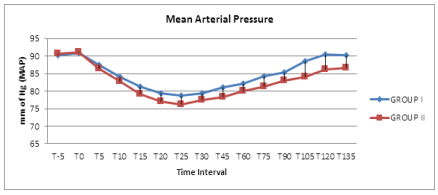
Table 3

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
TFRA	I	60	272.08	16.372	2.114	0.000
	II	60	298.67	14.754	1.905	
TIME PERIOD FOR FIRST RESCUE ANALGESIA (TFRA) (IN MINUTE)						

The time period for first rescue analgesia in Group I is 272.08 minutes. For Group II it is 298.67 minutes. p value is 0.000. This is highly significant statistical difference.



There were no significant difference between heart rates of both the groups .



MAP in both the groups were comparable upto 20 minutes from the induction time .. But after 20 minutes, there was statistical significant difference in both the groups.

Discussion –

In our study, we assessed the efficacy of two low doses of clonidine (15 mcg and 30 mcg) as an adjuvant to hyperbaric bupivacaine in spinal anaesthesia, in terms of onset and duration of sensory and motor blockade. We also compared duration of analgesia, and occurrence of side effects such as hypotension, bradycardia, and sedation. A total of 120 adult patients of either sex posted for lower limb orthopedic surgeries fulfilling the inclusion criteria were chosen. They were divided into groups of 60 each. The demographic data in both the group were comparable and no significant difference was found in both the group.

We used intrathecal clonidine at dose of 15 mcg (Group I) and 30 mcg (Group II) along with the bupivacaine 15 mg based on study by Arora et al.[10] They compared clonidine at dose of 15 mcg and 30 mcg added to intrathecal bupivacaine 12.5 mg. They found clonidine 15 mcg and 30 mcg leads to prolonged duration of sensory, motor block as well as post-operative analgesia . However with 15 mcg clonidine, hemodynamic profile was stable as compared to 30 mcg.

In the present study, we found that the time of onset of sensory block at T10 level was early in group II (4.02 + 0.701 minutes) as compared to group I (4.42 + 0.696 minutes). (p=0.002) This denotes highly significant difference in both the groups. Our study results are in accordance with observations of various studies such as Arora et al[10] Dobrydnjov I et al[11] and L.Niem et al[12] : They inferred that the onset sensory block was markedly reduced by the addition of intrathecal clonidine .

The mean onset of motor block was early in group II (6.72 minutes) than group I (7.48 minutes). (p=0.000) I. Van Tuijl et al [4] also observed the same results while comparing onset of sensory and motor block , which are comparable with our study .

We observed total duration of sensory block was prolonged in group II (130.08 minutes) as compared to group I (122 minutes).(p=0.000, highly significant) Agarwal et al [13] had found same results with clonidine (15 mcg and 30 mcg) and were comparable with our study.

Duration of motor block in our study was prolonged in group II (200.67 minutes) as compared to group I (184.08 minutes) . (p=0.000) Arora et al [10] observed that with 30 mcg clonidine motor block was 171.60 $\pm$ 38.20 minutes , whereas for 15 mcg it was 115.20 $\pm$ 38.41 minutes . There was increase in motor block duration with clonidine in dose dependent manner.

This may be due to clonidine's intrinsic capacity to block conduction in C and A delta nerve fibres, which potentiates sensory and motor blockade. The activation of pre and post synaptic 2 adrenergic receptors and release of norepinephrine and acetylcholine in the spinal cord could be the second potential mechanism that prevents activity of neuron and substance P from being released in the dorsal horn of the spinal cord. All of this intensifies the nerve fibers conduction block. [10]

Singh RB et al[2] observed that addition of clonidine increases duration of the post operative analgesia. They used 50 mcg of clonidine in 3 ml of 0.5 % bupivacaine and found that time for first analgesic requirement was increased to 551.06 $\pm$ 133.64 min as compared to control (254.80 $\pm$ 84.19 min) .

The TFRA in group II (298.67 $\pm$ 14.75 minutes) was prolonged as compared to group I(272.08 $\pm$ 16.37 minutes) .(p=0.000) .Though we did not study the post operative analgesic requirement in 24 hours but previous studies found that analgesic requirement reduced post operatively in clonidine group as compared to bupivacaine alone.

Heart Rate - On comparing heart rates in both the groups, we found no statistical significant difference in the heart rates until the complete procedure (p value for all the compared heart rates is > 0.05)

Different studies which have compared the effect of different doses of clonidine on heart rate concluded that it could cause decrease in heart rate but can be clinically controllable. Bradycardia was observed in 3 patients in Group I and 5 patients in group II which was controlled with injection atropine 0.6 mg. On comparing incidences of bradycardia, it was not significant. (p=0.18)

Klimscha et al [14] observed significant fall in heart rate after giving 150 mcg of clonidine intrathecally, whereas Bajwa et al [15] did not report it as they used clonidine only up to 45 mcg . So from our study result and previous studies, we could say that bradycardia from clonidine is dose dependent and lower doses do not affect the heart rate significantly.

Mean Arterial Pressure – There was decrease in MAP in both the group as compared to base line , however it was not significant till 20 th minute post induction . After that the fall in group II was more than in group I and was statistically significant . However, only 5 patients in group I and 7 patients in group II had one episode of hypotension which was treated with I.V injection ephedrine 6 mg. On comparing, it was not statistically significant. So our results are in accordance with the Sia et al [16] study results which also reported that 30 mcg of clonidine affect MAP more than that of 15 mcg of clonidine.

In our study, we ensured adequate preloading prior to subarachnoid block and optimal intra-operative volume replacement. Thus observed relatively stable haemodynamics in both the groups with regard to variation in mean arterial pressure from base line. Niem L et al [12] using doses of 3 mcg/kg of clonidine , higher dose than in our study, found significant drop in mean arterial pressure.

Higher doses of clonidine resulted in noticeably higher sedation scores. Kothari et al [17] observed that 35 % to 45 % of patients were drowsy when 50 mcg of clonidine was added to bupivacaine . According to various studies, clonidine significantly reduces the electroencephalogram's theta, alpha, and beta bands power. This hypnotic reaction might be mediated via the locus coeruleus, which has alpha-2 adrenergic receptors. In our study, 3 patients in group I and 4 patients in group II developed sedation. However, sedation score in all the patients was 2 or 3. On comparing both the groups, it was not statistically significant.

Limitations of our study - we did not include control group in our study and our study had only ASA I and ASA II patients .

Conclusion-

Though the incidence of hypotension were more with 30 mcg clonidine, it was not statistically significant. So we conclude that 30 mcg was better than 15 mcg in prolonging the sensory block, motor block and duration of analgesia, with no significant adverse effect in ASA I and ASA II patients.

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